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CHAPTER 12

Riot Control Agents

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I. INTRODUCTION

Nonlethal agents are a broad class of compounds intended to produce transient incapacitation of an individual or individuals. Both incapacitating agents and riot control agents (RCA) are separate classes of nonlethal agents. Although the two classes share the characteristic to incapacitate, a distinction must be drawn between these two types of agents. RCAs differ from incapacitating agents in several respects. RCAs possess a relatively short onset and limited duration of action. RCAs induce short-term toxic effects that subside within minutes following termination of the exposure. Additionally, modern RCAs have a very high safety ratio compared to incapacitating agents and first generation RCAs. Many incapacitating agents were developed during the Cold War which produced either limited lethality and/or prolonged morbidity. Consequently, incapacitating agents have been banned by international treaties recognized by the USA, including the Chemical Weapons Convention (CWC). Specifically, the CWC has placed a ban on the development, production, and possession of any chemical weapon intended to cause death or "temporary incapacitation". The USA considers these broad incapacitating agents as chemical warfare agents (CWAs). However, the USA does not recognize RCAs as CWAs, and therefore, US policy considers them to be legal for use by civilian police or the military. The CWC does prohibit their use in times of war. Thus, the USA has opted not to utilize RCAs in Iraq during the early 21st century against organized and armed insurgents.

While the field of nonlethal agents is diverse and interesting, we will limit our discussion to only those agents considered to be RCAs. The goal of RCAs is to temporarily incapacitate through irritating the skin and mucosal membranes of the eyes, airways, and digestive tract. As a result of their short-term toxicity, they are effective agents used by military and law enforcement personnel to disperse crowds, clear buildings, and quell riots. While RCAs are often thought of as "tear gas" or pulmonary irritants, they encompass more than this terminology would suggest. They are neither gases nor exclusively pulmonary irritants. Historically, RCAs were categorized as lacrimators, sternutators, and vomiting agents based upon their predominant toxicity on the eyes, lungs, or digestive tract. This nomenclature is outdated since modern RCAs affect a wide variety of organ systems. This fact will be clearly evident in the subsequent discussion concerning their mechanism of action and toxicity. Today, RCAs comprise a diverse array of chemical compounds with similar toxic effects since their introduction on the battlefield in the early part of the last century.

II. HISTORY

The Chinese were perhaps the first to employ pulmonary irritants with their stink bombs (Smart, 1996). The smoke emanating from them was a primitive sternutator designed to harass the enemy. RCAs were used during the 5th century BC Peloponnesian War when the Spartans used smoke from burning coal, sulfur, and pitch to temporarily incapacitate and confuse occupants of Athenian strongholds (Thoman, 2002). During antiquity, the Romans used irritant clouds to drive out their Spanish adversaries from hidden dwellings (Robinson, 1971). Almost all of these examples involved the use of incapacitating agents as an offensive tactical weapon as opposed to controlling crowds for defensive purposes.

World War I (WWI) marked the birth of RCAs as well as the modern age of CWAs (Figure 12.1). Both German and French forces used a wide variety of irritating agents, such as acrolein (papite), chloropicrin (PS), and diphenylaminearsine (DM; Adamsite); however, bromoacetone (BA) was the most widely used lacrimator agent at that time. At the end of WWI, the US military investigated the use of chloroacetophenone (CN) as a chemical irritant. First developed by Graebe in 1869 and formulated as Chemical Mace®, CN was the most widely used RCA up until World War II (Olajos and Stopford, 2004).

Two chemists, Carson and Stoughton (1928), synthesized 2-chlorobenzylidene malononitrile (CS); however, it was not adopted by the military as an official RCA until 1959. As a more chemically stable compound and having a greater potency with less toxicity than CN, it gradually replaced CN as the preferred RCA. CS was widely used during the Vietnam War to flush the Viet Cong out of the

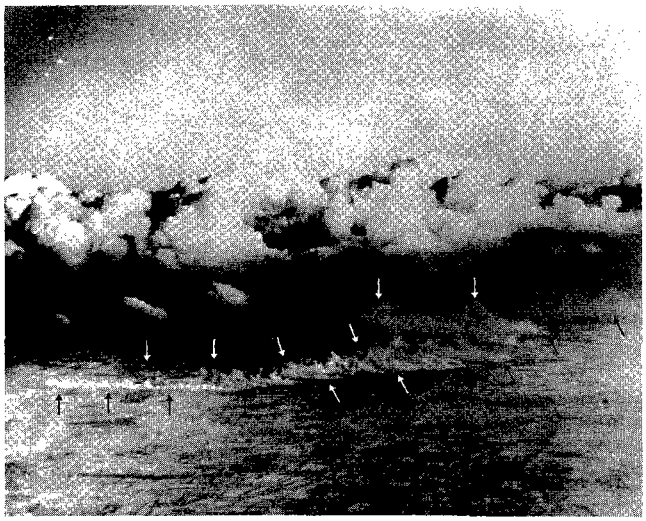

FIGURE 12.1. The birth of chemical warfare agents in World War I. The photograph depicts the initial chlorine gas attack by Germany at Ypres, Belgium, on April 22, 1915. The German Army released chlorine gas from cylinders to form a poisonous cloud (indicated by black and white arrows) directed toward the French lines by the prevailing winds. Photograph: courtesy of the US Army, Chemical Warfare Service, Edgewood, MD.

FIGURE 12.2. *Top*: US Army Engineers unpack and test a Mitey-Mite blower in the jungles of Vietnam. The Mighty-Mite aerosolized and dispersed smoke, CS powder, or other RCA as a means of tunnel denial. Photograph: courtesy of the US Army Engineer School, Fort Belvoir, VA. *Bottom*: American soldiers ("tunnel rats") wearing M28 protective masks just prior to entry into underground tunnels previously saturated with CS. Photograph: courtesy of the US Army Research Development and Engineering Command, Historical Research and Response Team, Aberdeen Proving Ground, MD.

labyrinth of underground tunnels and bunkers throughout Southeast Asia (Figure 12.2). In the years following the Vietnam War, other militaries adopted CS. Saddam Hussein's forces used it against Iran during the Iran–Iraq War of the 1980s. Today, CS is commonly used by law enforcement agencies and militaries for riot control training, respirator training in boot camps, temporary incapacitation of an assailant, and civil disturbances. A famous case of RCA use by the US Federal government involved CS dissemination on the Branch Davidian cult members in 1993. Because of its high flammability rating, CS was believed to be a large contributor to the inferno that burned down the Waco, Texas, compound and its inhabitants. Even before fire broke out and destroyed the compound, it is believed that CS concentrations ranged from five to 60 times the amount required to deter individuals (Bryce, 2000).

During the 1980s and 1990s, the use of CS gas was rapidly on the decline and slowly being replaced by oleoresin capsicum (OC) spray. OC, an extracted resin from *Capsicum* pepper plants, was first developed in the 1970s as an alternative to CN and CS agents. Commercially available OC sprays used by the public are approximately 1% capsaicin, while formulations used by law enforcement agencies can contain up to 15% capsaicin. Most recently, a synthetic form of capsaicin called nonivamide, marketed as Captor, gained popularity as a defensive aerosol in the early 1990s (Olajos and Stopford, 2000).

Under the CWC of 1997, RCAs were banned from use as a method of warfare because in high concentrations RCAs are toxic chemicals with the potential to incapacitate individuals for prolonged periods, produce long-term sequelæ, and cause death. The CWC allows RCAs to be used in domestic riot control, as well as enforcement of domestic law and "extraterritorial law enforcement activities undertaken by military forces" (Rosenberg, 2003). These boundaries and definitions, while vague, were clarified in 2003 by President George W. Bush (Wade and Schmitt, 2003). Bush authorized the use of tear gas against Iraqi troops for defensive purposes as allowed in Executive Order 11850 of 1975. Many experts believed this would violate the CWC (which was not signed by Iraq) and give Saddam Hussein the power to use chemical agents against the US under the authority of the Geneva Protocol (Wade and Schmitt, 2003). In the end, RCAs were never used during that conflict.

III. BACKGROUND

A. The Agents and Their Physicochemical Properties

Unlike the majority of chemical agents which are liquid at room temperature, modern RCAs are crystalline solids with low vapor pressure (see Table 12.1). RCAs are typically administered as fine particles, aerosol sprays, or in solutions; therefore, they are not true gases. The inhalation toxicity of RCAs, as well as CWAs, is often indicated by the expression Ct. This term is defined as the product of concentration (C) in mg·m^{-3} multiplied by exposure time (t) in minutes (mg·min m^{-3}). LCt_{50} and ICt_{50} are conventional terms used to describe airborne dosages that are lethal (L) or incapacitating (I) to 50% of the exposed population. The intolerable concentration (mg/m^3), ICt_{50} and minimal lethal concentration (mg/m^3) are provided in Table 12.1 for the most common RCAs. The ocular irritancy threshold (minimal irritant or minimal effective dose), estimated human LCt_{50}, and safety ratio are provided in Table 12.2 for these same RCAs. The modern RCAs are characterized by a high LCt_{50}, low effective Ct_{50}, low ICt_{50}, low minimal irritating concentration and large safety index ratio (LCt_{50}/irritancy threshold). As a rule of thumb, clinical signs and symptoms from RCA exposure generally subside within 30 min but may persist depending on dose and duration of exposure (Blain, 2003). Ortho-chloroacetophenone (CN) and chlorobenzylidene malononitrile (CS) are the classic representative agents of this class of compounds. The toxicity of CN and CS will be discussed in depth due to the vast volume of literature available for these compounds.

1. Chloroacetophenone (CN)

CN is a crystalline solid with a strong, pungent odor (see Figure 12.3). It is dispersed as a smoke, powder, or liquid formulation from grenades or other devices. It is perhaps better known under the trade name Chemical Mace® and was once used widely for self-protection. It was also the standard tear gas used by the military (Figure 12.4) and police personnel. It has been replaced in favor of the less toxic CS for riot control and capsaicin pepper spray for self-defense.

CN exhibits the greatest toxicity among RCAs in use today. Consequently, it has been replaced by compounds with higher safety ratios. CN is three- to ten-fold more toxic than CS in rats, rabbits, guinea pigs, and mice (Ballantyne and Swanston, 1978). Pathological findings in the lungs tend to be more severe and CN causes far greater edema. CN typically causes an acute, patchy, inflammatory cell infiltration of the trachea, bronchi, and bronchioles, in addition to early bronchopneumonia. CN not only demonstrates greater irritation to the skin than CS, it is also a more potent skin sensitizer (Chung and Giles, 1972). Patients frequently exposed to CN are at a high risk of developing allergic dermatitis (Penneys, 1971).

2. Ortho-chlorobenzylidene Malononitrile (CS)

The term CS was adopted after the two chemists, Carson and Stoughton, who synthesized the compound. CS is a white, crystalline powder with a pepper-like odor and low vapor pressure (see Figure 12.5). It is rapidly hydrolyzed following contact with water but minimally soluble in ethyl alcohol. CS is the most widely used RCA today, although many countries are switching to even less toxic compounds. CS is used by the US Armed Forces for gas discipline training exercises to help new recruits learn the importance of donning their protective masks quickly (Figure 12.6). It was also used by the USA during the Vietnam War for tunnel denial and crowd control (Figure 12.7) and by police forces for dispersing violent protests and incapacitating assailants.

3. Dibenz(*b,f*)-1:4-Oxazepine (CR)

Dibenz(*b,f*)-1:4-oxazepine (CR) (see Figure 12.8) is a potent sensory irritant with less toxicity than CS or CN (Ballantyne, 1977b). CR causes an immediate and effective irritation of the eyes, nose, and skin without persistent effects in these target organs. The irritation associated with CR is more transient compared to other RCAs. It is five to ten times greater in potency than CS; therefore, a smaller concentration is needed to cause irritation (low minimal irritant concentration or dose) and incapacitation (low ICt_{50}) (see Tables 12.1 and 12.2). CR has a favorable safety ratio; it is safer than other RCAs based on its higher LCt_{50} (Table 12.1) and greater LCt_{50}/irritancy threshold (safety ratio). In humans, the effects caused by CR are identical to CS. The LCt_{50} for humans is estimated at >100,000 mg.min/m^3. Despite its reduced toxicity in man, CR is not entirely without risk. CR is fairly stable, resists weathering, and persists in the environment (Sidell, 1997); therefore, enhanced toxicity may occur with prolonged exposure.

4. Diphenylaminechlorarsine (DM)

Diphenylaminechlorarsine (DM) (see Figure 12.9) or Adamsite are pro-emetic agents used in WWI. DM has greater toxicity than other RCAs and has been abandoned in favor of compounds with less toxicity and greater safety ratios. While toxicity is typically delayed with DM exposure, toxic signs and symptoms can occur within minutes after exposure. Systemic toxicity may also be more pronounced and prolonged. Symptoms often subside hours after exposure. Because DM is an antiquated RCA, this compound is irrelevant today and will not be discussed further.

5. Oleoresin Capsicum (OC)

Oleoresin capsicum (OC) is an oily resin derivative from capsicums and composed of several related compounds. Capsicums are solanaceous (nightshade species) plants from the genus *Capsicum*. More than 20 species fall within the genus. Capsaicinoids are considered the active ingredients of OC. These active compounds are endocrine products of glands found in the plant placenta and are a mixture of two unsaturated and three saturated homologs

TABLE 12.1. Physical characteristics and toxicity data for the common RCAs

		Physical characteristics			Toxicity data			
Agent	**Discovered in**	**Solubility**	**Vapor pressure (mm Hg @ 20°C)**	**Vapor density**	**Onset**	**Intolerable concentration (mg/m^3)**	**ICt_{50} ($mg \cdot min/m^3$)**	**Minimal lethal concentration[g] (mg/m^3)**
CS	1928 (Carson and Stoughton)[a]	Insoluble in water Soluble in organic solvents	0.00034	6.5	Immediate	5	3–10	2,500
CN	1871 (Graebe)[b]	Poorly soluble in water	0.0054	5.3	Immediate	35	20–40	850–2,250
DM	1915 (Wieland)[c] and 1918 (R Adams)[d]	Insoluble in water Poorly soluble in organic solvents except acetone	2×10^{-13}	9.6	Delayed with long recovery period	5	22–150	1,100–4,400
CR	1962 (Higginbottom and Suschitzkey)[e]	Sparingly soluble in water Stable in organic solvents	0.00059	6.7	Immediate	1	1	10,000
Bromobenzyl cyanide (CA)	1881 (Riener)[f]	Insoluble in water Soluble in organic solutions	0.12	4.0	Immediate	0.8	30	1,100

References: Maynard (1999); Sidell (1997); Smith and Stopford (1999); Olajos and Salem (2001).
[a]Carson and Stoughton (1928)
[b]Graebe (1871)
[c]Wiegand (1915); Wieland and Rheinheimer (1921)
[d]Sartori (1939)
[e]Higginbottom and Suschitzky (1962)
[f]Prentiss (1937)
[g]Estimate for minimal lethal concentration (10 min exposure)

TABLE 12.2. Health risk considerations for the common RCAs

Agent	Irritancy threshold[a] (mg/m^3)	Estimated human LCt_{50}[c] ($mg \cdot min/m^3$)	Safety ratio[d]	Adverse effects
CN	0.3[a]	8,500–22,500	28,000	Danger of permanent eye injury, vesiculation, bronchopneumonia, reactive airways, documented fatality cases
CS	0.004[a]	25,000–150,000	60,000	Same as CN, but fatality cases not authenticated, enhanced persistence compared to CN and CS
CR	0.002[a]	100,000	100,000	No significant respiratory toxicity
OC	0.0003[b]	not available	>60,000	Eye, skin, respiratory toxicity, significant morbidity in neonate, fatality involving case of in-custody use
DM	~1 [a]	11,000–44,000	11,000	No longer used
CA	0.15[a]	11,000	11,000	Predominantly a lacrimatory agent, no longer used

[a]Ocular irritancy thresholds unless indicated otherwise
[b]Threshold for respiratory complaints by capsaicinoids: Stopford and Sidell (2006); Lankatilake and Uragoda (1993)
[c]Values obtained from references: Maynard (1999); Sidell (1997); Smith and Stopford (1999); Olajos and Salem (2001)
[d]Values derived from estimate of the human LCt_{50} (lower bound)/irritancy threshold (minimal effective dose). Therefore, ranges are not provided for the safety ratios

(see Figure 12.10). Capsaicinoids are isolated through a volatile solvent extraction of the dried, ripened fruit of chili peppers. The capsaicinoids are distilled, dried, and compounded together. The final oleoresin contains several branched-chain alkyl vanillylamides, in addition to capsaicin, the major component in OC. The predominant capsaicinoid components of OC are capsaicin (70%), dihydrocapsaicin (20%), norhydrocapsaicin (7%), homocapsaicin (1%), and homodihydrocapsaicin (1%) (Salem *et al.*, 2006; see Figure 12.10).

Capsaicinoids cause dermatitis as well as nasal, ocular, pulmonary, and gastrointestinal effects in humans. OC gained popularity in the 1990s as a defensive weapon for civilians and law enforcement agencies because they produce an immediate, temporary immobilization and incapacitation when sprayed directly into the face or eyes. It is important to note that hand-held pepper spray formulations can contain OC by themselves or a mixture of OC and CS.

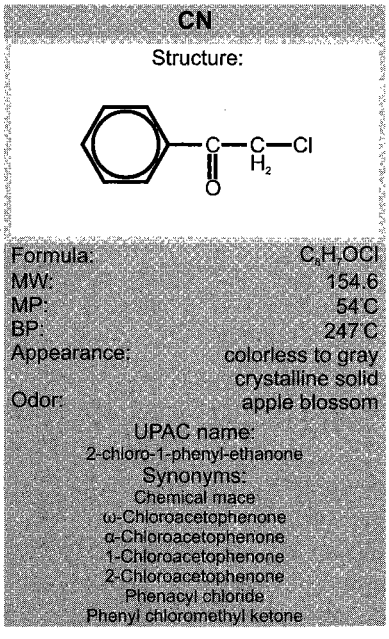

FIGURE 12.3. Chemical structure and physicochemical properties of chloroacetophenone (CN).

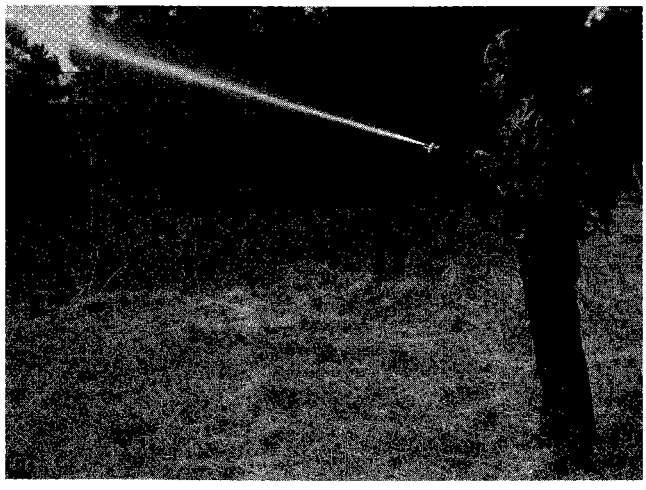

FIGURE 12.4. US soldier in protective clothing disseminating CN aerosol using the M33A1 disperser. Photograph: courtesy of the US Army Research Development and Engineering Command, Historical Research and Response Team, Aberdeen Proving Ground, MD.

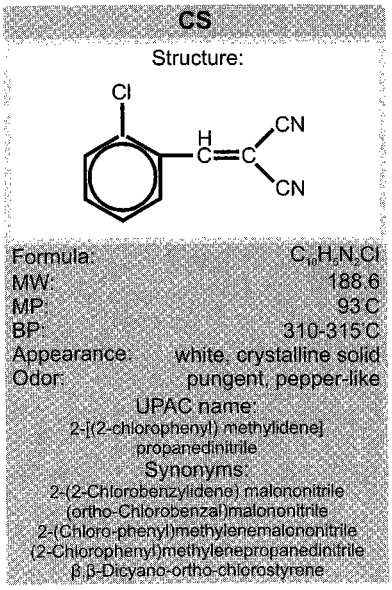

FIGURE 12.5. Chemical structure and physicochemical properties of ortho-chlorobenzylidene malononitrile (CS).

6. Pelargonic Acid Vanillylamide (PAVA)

Other capsaicinoids are available. Pelargonic acid vanillylamide (PAVA or nonivamide), shown in Figure 12.10, is a "synthetic" form of capsaicin. Nonivamide was first synthesized by Nelson (1919). Nonivamide was originally found to be a minor component in *Capsicum annum* peppers (Constant and Cordell, 1996); however, the majority of PAVA is derived from synthesis rather than extraction from natural plant sources. As a result, the composition and concentration of PAVA can remain consistent (Haber *et al.*, 2007).

FIGURE 12.6. Aerial spraying of a Chemical Warfare School class with CS tear gas during a training event. Photograph: courtesy of the US Army Research Development and Engineering Command, Historical Research and Response Team, Aberdeen Proving Ground, MD.

FIGURE 12.7. US Army soldiers using CS tear gas in South Vietnam. Photograph: courtesy of the US Army Research Development and Engineering Command, Historical Research and Response Team, Aberdeen Proving Ground, MD.

In order for PAVA to work, it must be directed at the subject's eyes. The pain to the eyes is reported to be higher than that caused by CS tear gas (Smith *et al.*, 2004; ACPO, 2006). The effects are immediate but will subside 15–20 min after exposure to fresh air. PAVA does display disadvantages. While PAVA has a high rate of effectiveness, it has proven to be ineffective against those under the influence of alcohol (ACPO, 2006). Additionally, the Smith *et al.* (2004) study mentions a number of cases where PAVA was used without effect. The effect of PAVA was also reported to be almost instantaneous, with the undesirable effect that recovery was also immediate. PAVA is commercially available in two forms, Captor I and Captor II. Captor I contains 0.3% PAVA with a solvent of equal parts ethanol and water. Captor II contains 0.3% PAVA with propylene glycol, water, and ethanol (COT, 2007).

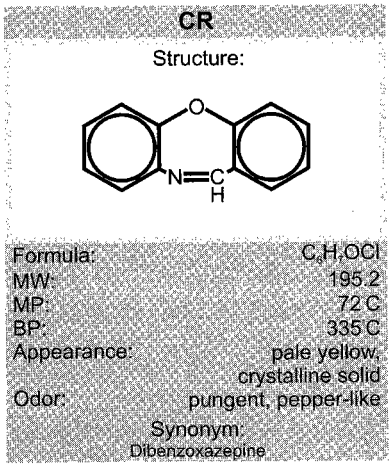

FIGURE 12.8. Chemical structure and physicochemical properties of dibenz(b,f)-1:4-oxazepine (CR).

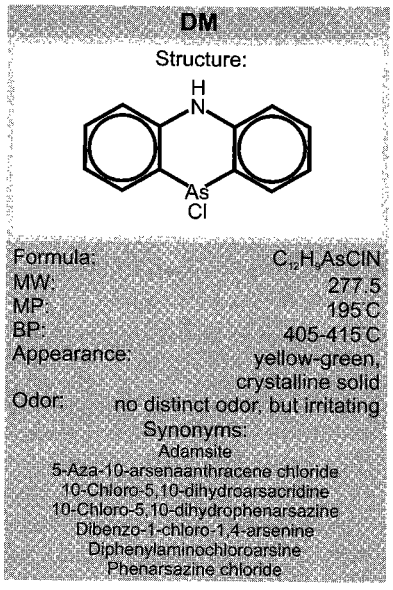

FIGURE 12.9. Chemical structure and physicochemical properties of diphenylaminechlorarsine (DM).

IV. MECHANISM OF ACTION

A. CS, CN, and CR

The mechanisms of action through which RCAs act are not completely understood. One explanation for the toxic effects of RCAs is the production of hydrochloric acid through reduction of chloride ions on mucosal membranes (Worthington and Nee, 1999). This may help explain the marked, focal irritation and burns on skin resulting from exposure to CS (Anderson *et al.*, 1996). In addition, CS and CN are SN_2 alkylating agents (Cucinell *et al.*, 1971; Ballantyne and Swanston, 1978); in contrast, the vesicant mustard is an SN_1 alkylating agent. The SN_2 moniker describes direct reaction of the agent with nucleophilic compounds in a bimolecular fashion. In particular, they react with intracellular thiol or SH-containing enzymes, thereby inactivating them (Ballantyne, 1977a). Mackworth (1948) first showed that CN and other first generation lacrimators used during WWI (bromoacetophenone, ethyl iodoacetate, chloropicrin, bromobenzyl cyanide) strongly inhibited thiol-containing succinic dehydrogenase and pyruvic oxidase, major players of crucial metabolic pathways. Some suggest that lactic dehydrogenase is completely insensitive to lacrimators (Mackworth, 1948), but only lacrimators from the iodoacetate family were ever studied by this group. Another group reported that lactic dehydrogenase is in fact strongly inhibited by CS (Cucinell *et al.*, 1971). Chloropicrin also interferes with oxygen transport to the tissues by reacting with SH groups on hemoglobin.

In addition, CS reacts with the disulfhydryl form of lipoic acid, a coenzyme in the pyruvate decarboxylase system (Olajos and Salem, 2001). Alteration in dihydrolipoic acid biochemistry can lead to decreased acetyl CoA levels, resulting in cellular injury. Therefore, tissue injury seems to be related to inactivation of these metabolic enzyme systems. The damage is transient because the enzymes can be rapidly reactivated if exposure is terminated (Beswick, 1983).

Based on these studies, it has been suggested that alkylation of nucleophilic sites, including SH-containing enzymes, is the underlying biochemical lesion responsible

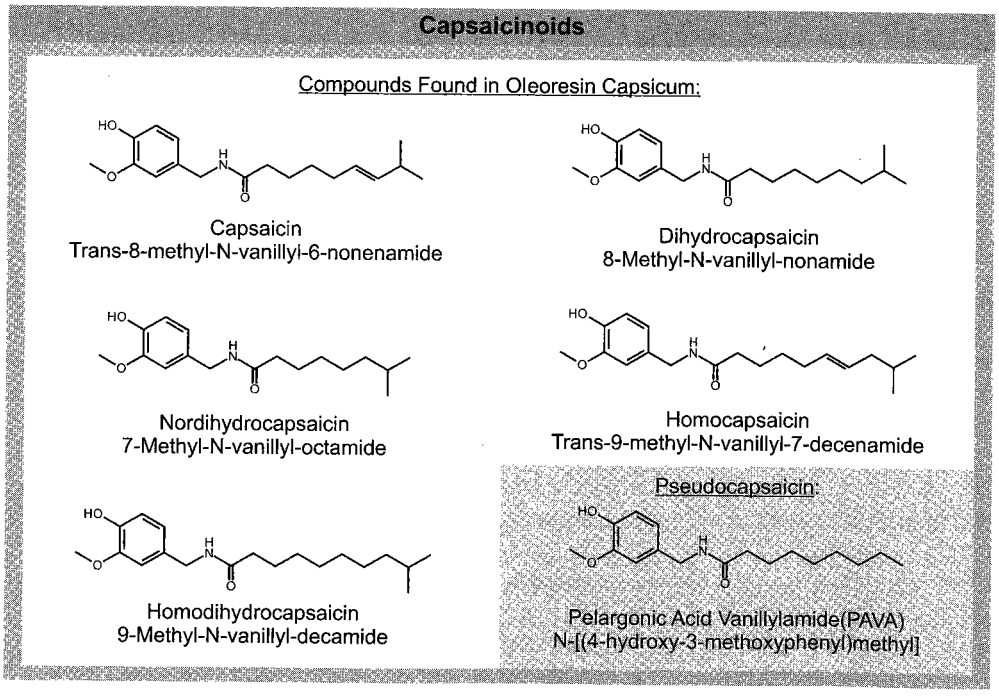

FIGURE 12.10. Chemical structures of the most common capsaicinoids found in oleoresin capsicum.

for lacrimator-induced toxicity. However, pain from RCA exposure can occur without tissue injury. It has been suggested that the irritant and painful effect of CS may be bradykin mediated (McNamara *et al.*, 1969; Cucinell *et al.*, 1971; Olajos and Salem, 2001). CS causes bradykinin release *in vivo* in humans (Cucinell *et al.*, 1971) and *in vitro* (Blain, 2003). Elimination of bradykininogen *in vivo* abolishes the systemic response to CS (USAMRICD, 2000; Salem *et al.*, 2006).

The metabolism of CS to cyanide (see section V) was once thought to be responsible for agent-induced lethality in animals (Cucinell *et al.*, 1971; Jones and Israel, 1970). Despite reports on alleged fatality cases, mortality in humans following CS administration has not been authenticated (Ballantyne, 1977a; Hill *et al.*, 2000; Olajos and Salem, 2001). CS has been demonstrated to cause death in dogs (Cucinell *et al.*, 1971). CS is hydrolyzed to malononitrile and 2-chlorobenzaldehyde (Brewster *et al.*, 1987). Further metabolism of malononitrile yields two potential cyanides, which could interact with sulfur thiols to yield thiocyanate. Cyanide typically causes death immediately, but animals administered CS by inhalation far above the lethal *Ct* do not die immediately; death occurs 12 to 24 h after exposure. In fact, death seems to be due to airway and lung damage (Ballantyne and Swanston, 1978; Ballantyne and Callaway, 1972). Studies to ascertain cyanide production after CS exposure in humans showed negligible levels of plasma thiocyanate (Swentzel *et al.*, 1970; Leadbeater, 1973). Another study revealed low levels of cyanide production in mice administered carbon 14-labeled CS (Brewster *et al.*, 1987). In short, cyanide is not liberated in sufficient quantity from CS metabolism to become toxic enough to cause death.

While cyanide inhibition of cytochrome *c* oxidase may not account for the full spectrum of toxicity in CS exposure, cyanide toxicity may include an array of biochemical interactions (Way, 1984). These include lipid peroxidation (Johnson *et al.*, 1987), cyanide release of endogenous opioids to cause respiratory paralysis (Leung *et al.*, 1986), disruption of neuronal calcium homeostasis (Johnson *et al.*, 1986), and phospholipids hydrolysis (Sakaida and Farber, 1990). The mechanism of action for CN follows very closely that of CS as they are both alkylating agents. The effect of both agents on SH-dependent enzyme systems has been studied (Lovre and Cucinell, 1970; Cucinell *et al.*, 1971). Less is known regarding the mechanism of action for CR intoxication.

B. Capsaicinoids

Capsaicinoids interact with a population of neuropeptide-containing afferent neurons and activate a "vanilloid" receptor (Szallasi and Blumberg, 1990, 1992; Szallasi *et al.*, 1991). There seems to be a requirement by the receptor for a vanilloid ring and an acyl chain moiety for activity (Szallasi and Blumberg, 1999; Caterina and Julius, 2001). Vanilloid receptors are part of a superfamily of transient receptor potential (TRP) cation channels (Montell *et al.*, 2002). Binding of a vanilloid-containing ligand to the receptor causes channel opening, influx of Ca^{2+} and Na^{+}, depolarization of the neuron, and release of neuropeptides (Lundblad and Lundberg, 1984; Martling, 1987). In addition to transitory excitation of primary afferents, activation of these receptors leads to a prolonged refractory period, indicative of an apparent nonconducting, desensitized state of the receptor. In this refractory period, primary afferents become unresponsive to further application of capsaicinoids. Furthermore, it has been suggested that influx of Ca^{2+} and Na^{+} may lead to rapid cellular damage and eventual cell death (Jancso *et al.*, 1984), possibly by Ca^{2+}-dependent protease activity. Administration of capsaicin in neonatal rats causes destruction of the dorsal root ganglion neurons (Jancso *et al.*, 1977).

The biological actions of capsaicin are primarily due to release of the neuropeptide substance P, calcitonin gene-related peptide (CGRP), and neurokinin A from sensory neurons. These transmitters from primary sensory neurons communicate with other cell types. They produce alterations in the airway mucosa and neurogenic inflammation of the respiratory epithelium, airway blood vessels, glands, and smooth muscle. Alterations in multiple effector organs lead to bronchoconstriction, increased vascular permeability, edema of the tracheobronchial mucosa, elevated mucosal secretion, and neutrophil chemotaxis (Lundberg and Saria, 1982; Lundberg *et al.*, 1983, 1984; Blanc *et al.*, 1991; Tominack and Spyker, 1987). Capsaicin-induced effects of bronchoconstriction, vasodilation, and plasma protein extravasation are mediated by substance P. In addition, substance P can cause bronchoconstriction through stimulation of c-fibers in pulmonary and bronchial circulation.

V. TOXICOKINETICS

The uptake, distribution, and metabolism of CS, CR, and capsaicins (but not CN) have been well characterized.

A. Uptake, Distribution, and Metabolism of CS

CS is rapidly absorbed and distributed throughout the body after inhalation exposure. Pharmacokinetic studies show that CS is removed from circulation quickly with first-order kinetics, following inhalation exposure. CS half-life is just under 30 s (Olajos, 2004). Short half-lives in the circulatory system are also demonstrated for the major CS metabolites (2-chlorobenzyl malononitrile and 2-chlorobenzaldehyde) (Leadbeater, 1973). Currently, it is thought that significant amounts of CS, near the tolerable concentration around 10 mg/m^3, would not be absorbed following CS inhalation. The absorption of CS from the digestive tract in cases of exposure by ingestion is unknown at this time. Systemic toxicity

has been noted after ingestion of CS pellets (Solomon *et al.*, 2003).

In mammalian species, CS rapidly hydrolyzes to form 2-chlorobenzaldehyde and malononitrile (Leadbeater, 1973; Paradowski, 1979; Rietveld *et al.*, 1986). The malononitrile intermediate is further metabolized from two cyanide moieties, which are converted to thiocyanate (Cucinell *et al.*, 1971). The aldehyde intermediate undergoes oxidation to 2-chlorobenzoic acid or reduction to 2-chlorobenzyl alcohol. These metabolites are conjugated and excreted in the urine.

B. Uptake, Distribution, and Metabolism of CR

Absorption of CR after aerosol inhalation is rapid with a plasma half-life of 5 min; this is consistent with half-life estimates following intravenous administration (Upshall, 1977) and gastrointestinal uptake (French *et al.*, 1983). Corneal tissue has been demonstrated to take up CR and metabolize it to the lactam derivative (Balfour, 1978; King and Holmes, 1997).

A number of studies have investigated the bioconversion, fate, and elimination of CR in various animal species (French *et al.*, 1983; Furnival *et al.*, 1983; Balfour, 1978; Harrison *et al.*, 1978). Human metabolic studies on CR have not been performed due to the high degree of sensitivity of human tissues to CR. The maximum tolerated dosage is far too low to allow for detection in metabolic studies (Olajos, 2004). The lactam derivative dibenz[*b,f*]1:4-oxazepin-11-(10H)-one is a primary metabolic product of metabolism and a direct precursor of the urinary hydroxylated metabolites. In rats, the lactam, a dihydro-CR metabolite, an amino alcohol of CR, and an arene oxide are metabolites in CR degradation. In the rat, the major mechanism for elimination is sulfate conjugation and biliary excretion to a limited extent. Phase I metabolism by microsomal mixed function oxidases involves reduction of CR to the amino alcohol, oxidation to form the lactam ring, and hydroxylation to form the hydroxylactams. Phase II conjugation reactions sulfate the hydroxylactam intermediates for renal elimination. Amino alcohol intermediates are conjugated with glucuronide for biliary secretion.

C. Uptake, Distribution, and Metabolism of CN

The uptake, distribution, and fate of CN have been poorly characterized despite numerous investigations reporting its toxicity. Inhalation of lethal CN, which does not metabolize to liberate cyanide, also causes death secondary to effects on the pulmonary system (pulmonary congestion, edema, bronchopneumonia, cellular degeneration in the bronchiole epithelium, and alveolar thickening) in mice, rats, guinea pigs, and dogs (Olajos and Salem, 2001). CN presumably reacts irreversibly with the free sulfhydryl groups of proteins and enzymes. It is thought that CN metabolically converts to an alkylating agent with this affinity for SH groups and nucleophilic sites in tissues (Mackworth, 1948; Olajos, 2004).

D. Uptake, Distribution, and Metabolism of Capsaicins

Capsaicin and capsaicinoids undergo Phase I metabolic bioconversion to catechol metabolites via hydroxylation of the vanillyl ring moiety (Lee and Kumar, 1980; Miller *et al.*, 1983). Metabolism involves oxidative, in addition to non-oxidative, mechanisms. An example of oxidative conversion involves the liver mixed-function oxidase system to convert capsaicin to an electrophilic epoxide, a reactive metabolite (Olajos, 2004). Surh and Lee (1995) have also demonstrated the formation of a phenoxy radical and quinine product; the quinine pathway leads to formation of a highly reactive methyl radical (Reilly *et al.*, 2003). The alkyl side chain of capsaicin also undergoes rapid oxidative deamination (Wehmeyer *et al.*, 1990) or hydroxylation (Surh *et al.*, 1995; Reilly *et al.*, 2003) to hydroxycapsaicin as a detoxification pathway. An example of nonoxidative metabolism of capsaicin is hydrolysis of the acid–amide bond to yield vanillylamide and fatty acyl groups (Kawada *et al.*, 1984; Oi *et al.*, 1992).

VI. TOXICITY

RCAs produce a wide variety of physiological effects in man. Figure 12.11 illustrates these generalized toxic signs and symptoms of exposure. The clinical effects in the figure are representative of those encountered after CN or CS exposure. CR causes qualitatively similar effects to those caused by CS, except it has greater potency. The predominant anatomical regions affected include eye, lung, and skin. RCAs also cause nasal, oral, neuronal, and gastrointestinal effects.

A. Ophthalmological Effects

1. CN and CS

The eyes are a major target for the short-lived toxic effects of RCAs. Eye findings from RCA toxicity can range in severity from conjunctival erythema to ocular necrosis. Lacrimation, conjunctival erythema/edema, blepharitis, and erythema are the most typical findings after exposure to all RCAs. Toxic signs may further include periorbital edema (Vaca *et al.*, 1996; Yih 1995), blepharospasm or spasms during eyelid closure (Grant, 1986; Blain, 2003), apraxia of eyelid opening, ophthalmodynia, corneal injury, and ocular necrosis (Grant, 1986). Figure 12.12 illustrates and summarizes the common toxic ophthalmological signs and symptoms associated with RCA aerosol exposure. It is important to note that eye findings tend to be more severe in

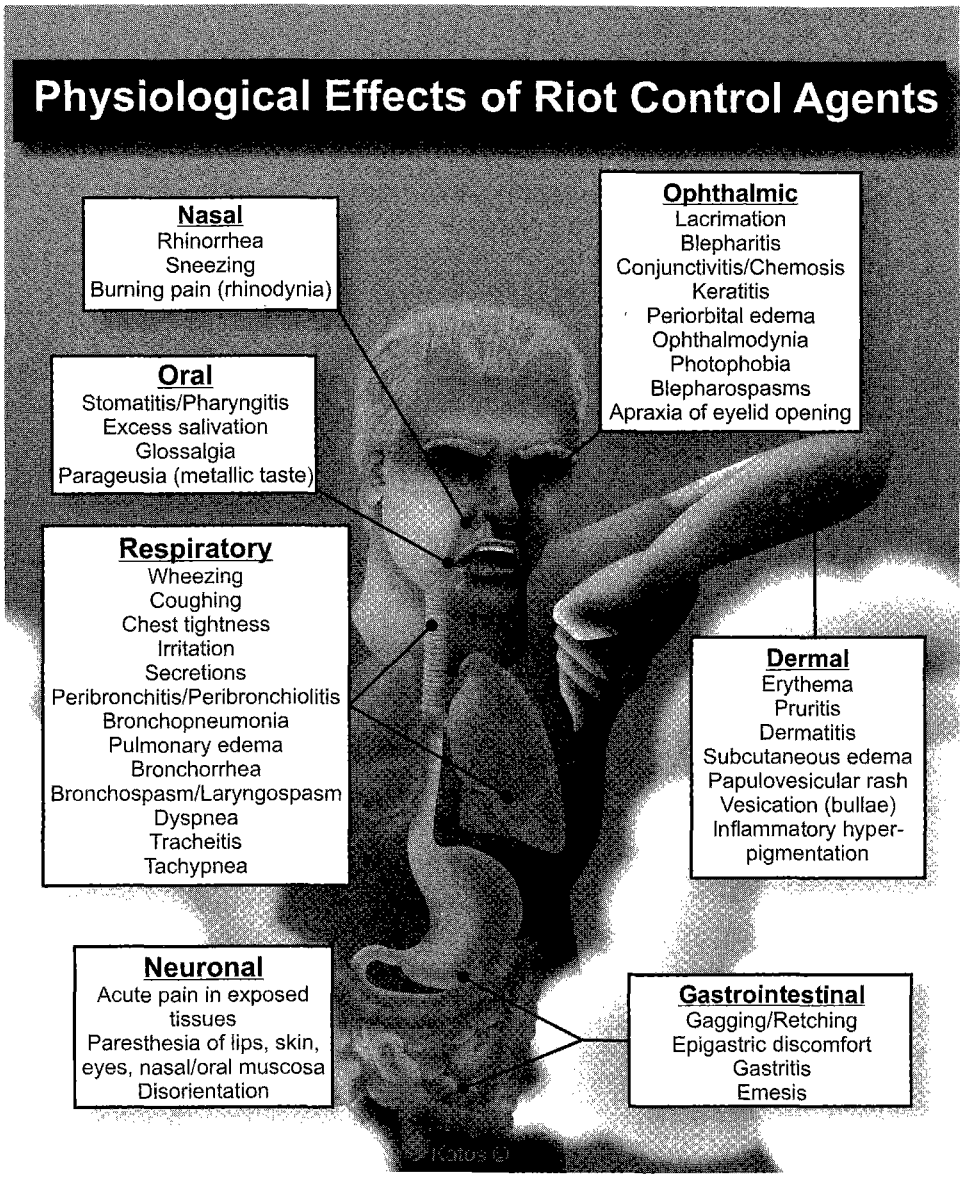

FIGURE 12.11. Physiological effects of riot control agents. Illustrated, copyright protected, and printed with permission by Alexandre M. Katos.

RCA exposure victims if they are wearing contact lenses (Solomon *et al.*, 2003).

Erythema and edema may last up to 48 h and vascularizing keratitis is not uncommon (Ballantyne *et al.*, 1974), but symptoms generally subside after 30 min (Beswick, 1983) depending on the concentration and duration of exposure (Blain, 2003). Recovery is typically complete within 15 to 30 min after exposure, but a few signs such as erythema of the lid margins and photophobia may persist slightly longer. The conjunctivae may appear injected or even progress to fulminant conjunctivitis and blurred vision following some RCAs including CS (Euripidou *et al.*, 2004). Toxic signs in the conjunctivae from CN Mace exposure can include conjunctivitis, sloughing, limbal ischemia, and symblepharon formation (adhesion of the eyelids to the eyeball) (Scott, 1995). Permanent eye injury is unlikely except after exposure to high concentrations of CN Mace (Grant, 1986). While permanent eye damage is uncommon, raised intraocular pressure from edema may precipitate acute angle closure glaucoma if left untreated. Long-term sequelæ may include cataracts, vitreous hemorrhage, and traumatic optic neuropathy (Gray and Murray, 1995).

In studies involving human exposure (Rengstorff and Mershon, 1969a, b), CS (0.1% or 0.25% in water; 1.0% in triocyl phosphate) sprayed or administered as ophthalmic drops onto the eyes, caused apraxia of eyelid opening with blepharospasm upon eyelid closure for 10 to 135 s. It also caused a transient conjunctivitis but no corneal damage upon further inspection with a slit lamp. Rabbit eyes contaminated with CS as a solution (0.5–10% in polyethylene glycol), as a solid, or thermally dispersed as a smoke (15 min at 6,000 mg/m^3) showed a greater toxicity with solution. CS in solution caused profuse lacrimation, conjunctivitis, iritis, chemosis, keratitis, and corneal vascularization at concentrations at or above 1%.

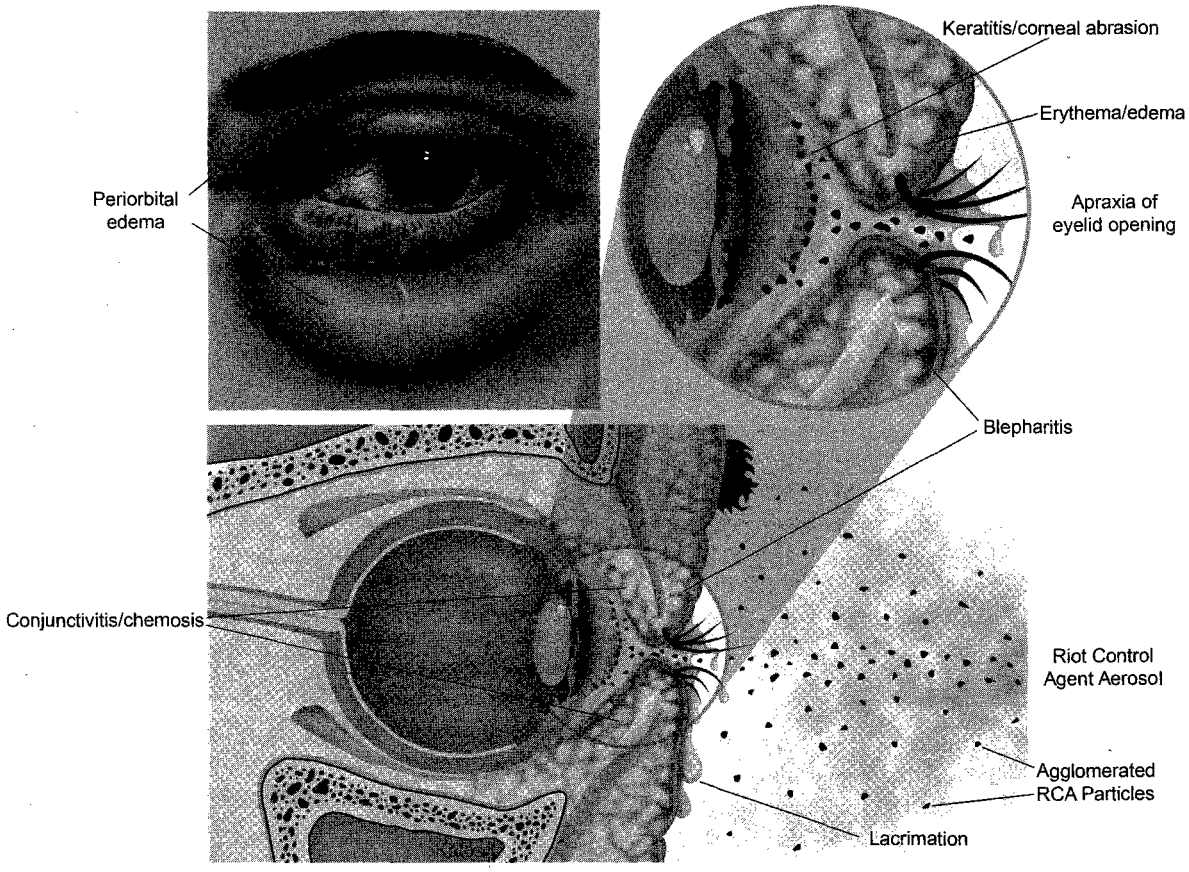

FIGURE 12.12. Exposure of the eye to CS aerosol. *Top left panel*: external view of left eye immediately after exposure to CS aerosol, showing scleral injection, periorbital edema, and lacrimation. *Bottom panel*: Penetration of CS aerosol into the eye, sagittal view. Following exposure to CS, the eye responds with inflammation, edema (chemosis), lacrimation, erythema, eye pain, and eyelid closure. *Top right panel*: Close-up of the eye and eyelids, sagittal view. Inflammation of the eyelids (blepharitis), conjunctivae (conjunctivitis), and cornea (keratitis) are apparent. The eye, in turn, responds with spasms of eyelid closure (blepharospasms) followed by an inability to open the eyelids (apraxia of eyelid opening). Agglomerated CS particles can penetrate the eye upon initial contact and cause corneal abrasions. Illustrated, copyright protected, and printed with permission by Alexandre M. Katos.

The lesions tended to be more severe and have a greater duration at higher doses. Histologically, the cornea appeared with patchy denudation of the epithelium and infiltration of neutrophils to the site of injury (Ballantyne *et al.*, 1974). In general, more severe eye exposures have resulted from CN compared to CS agent.

CN causes a similar constellation of ocular signs and symptoms as CS, but CN toxicity is likely to be more severe in the eyes and skin. CN sprayed into the eyes from a distance causes lacrimation, edema of the corneal epithelium and conjunctivae, and reversible epithelial defects of the cornea (Leopold and Lieberman, 1971). At close range, CN can cause long lasting and permanent damage to the eye. Because RCAs are solids, it is possible for a particle to clump or agglomerate, causing penetration into corneal or conjunctival tissues (see Figure 12.12). Agglomerated CN particles can penetrate eye tissue as a result of tear gas cartridge discharge (Levine and Stahl, 1968). In addition to large powder CN agglomerates, traumatic effects from the propellant charge, wadding, or foreign pieces from the cartridge should also be suspected when evaluating eye damage from CN.

While RCAs produce short-lived effects, rabbits exposed to 10% CN solution caused iritis and conjunctivitis >7 days and corneal opacity (Grant, 1986) lasting longer than 2 months (Gaskins *et al.*, 1972). In comparison, CS at the same concentration produced moderate conjunctivitis without iritis or corneal opacity, and eyes returned to normal by the end of one week. Another difference between the two agents is that CN produces a more severe reaction than CS when applied to the eye in powder form or as a spray at close range (McNamara *et al.*, 1968).

In addition to opacification, additional corneal effects from particulate CN exposure include possible penetration of the corneal stroma, severe scarring and ulceration, and deficits in the corneal reflex (Blain, 2003; Scott, 1995). Penetration of the corneal stroma may lead to stromal edema and later vascularization, resulting in further ocular complications. These may include pseudopterygium, infective keratitis, symblepharon, trophic keratopathy, cataracts,

hyphema, posterior synechia, secondary glaucoma, vitreous hemorrhage, and traumatic optic neuropathy (Hoffman, 1967). Furthermore, a 4% CN formulation produced permanent corneal injury while a 10% CS product did not (Gaskins *et al.*, 1972). In animal studies, high concentrations of CN produce ocular necrosis (Grant, 1986).

The eyes are also affected from CS agent without direct contact of the agent with the eye. In one report, seven patients were exposed to oral ingestion of a juice drink contaminated by CS pellets (Solomon *et al.*, 2003). In addition to mild headache and gastrointestinal irritation, patients complained of ocular irritation and lacrimation. The majority of symptoms resolved within 24 h of exposure.

2. CR

Higginbottom and Suschitzky (1962), the chemists who discovered CR, first noted the intense lacrimal response to this compound. A splash of CR (0.01 to 0.1% range solution) causes immediate ophthalmodynia, lacrimation, and blepharospasm, similar to CS and CN (Sidell, 1997). These effects can last 15 to 30 min before subsiding. Blepharitis (edema of the eyelids), periorbital edema, and injected conjunctivae can last for up to 6 h. In rabbits and monkeys, CR (0.1% solution) causes mild, transient erythema, chemosis, and keratitis in the eye. Moderate conjunctivitis has been demonstrated with higher CR concentrations (5% solution) applied directly to the rabbit eye (Rengstorff *et al.*, 1975). Ballantyne *et al.* (1975) showed that increasing CR concentrations as a solution caused dose-dependent corneal thickening but minor eye effects (mild conjunctivitis and lacrimation) as an aerosol. In animal studies, the effects of CR on the eye are very transient as they are cleared in 1 h, and it produces far less toxicity to the eye than CN (Salem *et al.*, 2006).

3. Capsaicin

Capsaicin causes conjunctivitis, periorbital edema/erythema, ophthalmodynia, blepharospasm, blepharitis, corneal abrasions, and lacrimation. In a retrospective study of 81 patients who presented to the emergency department following aerosol exposure from law enforcement use of OC, 56% of individuals developed ophthalmodynia, 44% conjunctivitis, 40% conjunctival erythema, 13% lacrimation, and 9% corneal abrasions (Watson *et al.*, 1996). Another study involved exposure of 47 human volunteers to OC for evaluating effects on the cornea and conjunctivae (Zollman *et al.*, 2000). All subjects reported significant eye pain, blurred vision, and lacrimation 10 min after exposure to OC pepper spray, but symptoms improved by 1 h later. Corneal abrasions were not apparent, but 21% of subjects showed evidence of punctate epithelial erosions and reduced corneal sensitivity. Corneal abnormalities were absent 1 week after exposure. Another human study identified 23% of subjects (7 of 30) with corneal abrasions following aerosol exposure to OC spray (Watson *et al.*, 1996). In mice, a single subcutaneous injection of 12.5, 25, or 50 mg/kg capsaicin causes corneal changes characterized by neuronal axon degeneration in the corneal epithelium (Fujita *et al.*, 1984).

B. Nasal/Pharyngeal Toxicity

RCAs produce oral and nasal symptoms immediately after exposure. Inhalation exposure to CN and CS causes rhinorrhea, sneezing, and burning pain within seconds (Beswick, 1983); a similar burning sensation with increased salivation occurs after oral contact with aerosolized powder or solution. The salivation, pharyngitis, and glossalgia occur within minutes after exposure (Thorburn, 1982; Beswick, 1983). A CR solution (0.01 to 0.1% range) splashed in the mouth causes salivation and burning of the tongue (Ballantyne and Swanston, 1974) and palate for several minutes. Splashes of the solution can cause nasal irritation and rhinorrhea (Sidell, 1997). Fumes from burned *Capsicum* plants or capsaicin-containing pepper sprays are highly irritating to the nasal mucosa and cause immediate rhinorrhea (Morton, 1971; Collier and Fuller, 1984; Geppetti *et al.*, 1988).

C. Cardiovascular Toxicity

While the evidence is not overwhelmingly impressive, RCAs have apparent effects on the cardiovascular system. Tachycardia and mild hypertension have been noted after exposure (Beswick, 1983). This response may result from anxiety or a response to the pain as opposed to any toxicological effect. The initial response to aerosolized CS is hypertension and irregular respiration, suggestive of the Sherrington pseudoaffective response. Bypassing the pain receptors of the nose and upper airway by endotracheal administration of CS leads to a decrease in blood pressure and bradypnea, effects also seen after intravenous injection. This suggests the initial pressor effect and irregular respiration are generalized responses to noxious stimuli rather than pharmacological effects of CS. Splash contamination of the face or whole-body drenching with dilute CR solution (0.0010 and 0.0025%) causes an immediate increase in blood pressure and bradycardia (Ballantyne *et al.*, 1973, 1976). Intravenous administration of CR in cats causes a transient but dose-dependent tachycardia. These pressor effects are postulated to be secondary to CR effects on sympathetic tone to the cardiovascular system (Lundy and McKay, 1975) or the result of stress and discomfort from the irritation (Ballantyne, 1977a, b).

RCAs have been shown to have a direct effect on the heart. One report linked exposure of high CS concentrations to the development of congestive heart failure (Hu *et al.*, 1989). Furthermore, underlying cardiac disease has been shown to exacerbate toxicity from CS (Worthington and Nee, 1999).

D. Respiratory Toxicity

CS and CN are disseminated as an aerosol powder or solution. Therefore, the most common route of CN or CS absorption is by inhalation. Inhalation of RCAs causes burning and irritation of the airways leading to cough, chest tightness, dyspnea (Beswick, 1983, Hu *et al.*, 1989; Blain, 2003), shortness of breath (Euripidou, 2004), bronchospasm (Hu and Christiani, 1992), and bronchorrhea (Folb and Talmud, 1989). Estimates of the minimal irritant exposure and ICt_{50} are 0.004 and 5 mg·min/m^3, respectively, for CS (Olajos and Salem, 2001). Similar estimates have been made for CN (0.3–1 and 20–50 mg·min/m^3; Olajos and Salem, 2001). Other estimates report that 31 mg/m^3 CN vapor is intolerable to humans after 3 min (Punte *et al.*, 1962).

Laryngospasm can occur either immediately or delayed for 1 to 2 days after CN or CS exposure. Delayed onset laryngotracheobronchitis 1–2 days post-exposure, characterized by wheezing, dyspnea, tachypnea, hoarseness, fever, and purulent sputum, was reported in three of eight patients exposed to high concentrations of CN (Thorburn, 1982). Long-term bronchodilator therapy was required in one patient with pre-existing pulmonary disease. Reactive airways are associated with high-level exposure to CS and CR (Blain, 2003). Paroxysmal cough, shortness of breath, and chest tightness, characteristic of reactive airway disease, have been demonstrated to last up to several weeks. Pulmonary effects typically resolve by 12 weeks post-exposure.

Pulmonary edema may occur up to 24 h post-exposure (Stein and Kirwan, 1964; Gonmori *et al.*, 1987). Gonmori *et al.* (1987) reported a fatality from chloropicrin spray intoxication. The patient, an 18-year-old female, developed pulmonary edema 3 h after exposure. Furthermore, a 43-year-old man developed pulmonary edema complicated by pneumonia, heart failure, and hepatocellular damage after CS intoxication (Krapf and Thalmann, 1981). Delayed onset bronchopneumonia may occur from prolonged exposure to some RCAs in enclosed spaces (Beswick, 1983).

There is no evidence that CS causes permanent lung damage after one or several exposures to field concentrations (Blain, 2003). Inhalation of an irritant might be expected to exacerbate underlying pulmonary disease such as asthma, emphysema, or bronchitis. Histories of asthma and chronic obstructive pulmonary disease may exacerbate effects from CS (Worthington and Nee, 1999) or CN (Thorburn, 1982). CS may exacerbate chronic bronchitis or precipitate an attack in known asthmatics (Anonymous, 1971).

1. CN and CS Toxicity in Animals

In animal studies, the cause of death from CN inhalation is the result of toxicity in the pulmonary system. Post-mortem examination from acute toxicity lethality studies in animals exposed to CN aerosols reveal pulmonary congestion, edema, emphysema, tracheitis, bronchitis, and bronchopneumonia in dogs and pulmonary congestion, edema, and bronchopneumonia in mice, rats, and guinea pigs (Olajos and Salem, 2001). Sublethal CN aerosol exposure (62.6 mg/m^3, 0.1 LC_{50}) for 60 min causes cellular degeneration in the bronchiole epithelium and alveolar septal wall thickening due to infiltration of mononucleocytes (Kumar *et al.*, 1995).

Exposure to aerosol CS (unreported concentration) in male Wistar rats for 20 min can cause decreased minute ventilation and induce histological lesions of the trachea (cytoplasmic vacuoles in epithelial cells) and lung (emphysema) (Debarre *et al.*, 1999). Lower respiratory tract injury, including fibrosing peribronchitis and peribronchiolitis, can be produced by chloropicrin (Buckley *et al.*, 1984).

2. CR

CR does not produce any significant respiratory toxicity (Sidell, 1997). CR causes tachypnea and labored breathing in multiple animal species. In humans, aerosol exposure to CR causes respiratory irritation, choking, and dyspnea. One human study involving aerosol exposure to CR (0.25 mg/m^3) in volunteers for 60 min noted decreased expiratory flow rate minutes after exposure. CR was thought to stimulate irritant receptors in the conducting portion of the pulmonary system, causing bronchoconstriction (Ashton *et al.*, 1978). Additionally, CR increased blood volume in the lungs by driving sympathetic tone. Two animal studies evaluated the effect of CR aerosol exposure on the physical and ultrastructural changes in rat lungs (Pattle *et al.*, 1974; Colgrave *et al.*, 1983). Even high CR aerosol doses did not produce significant pulmonary damage. Gross examination of the lungs was normal in both studies. Microscopic examination showed mild congestion, lobar hyperinflation characteristic of emphysema and hemorrhage. Further pulmonary damage was evident on electron microscopy. CR exposed lungs showed capillary damage of the endothelium and a thickened, swollen epithelial layer (Colgrave *et al.*, 1983).

3. Capsaicin

In children, capsaicin spray was demonstrated to cause a severe bronchospasm and pulmonary edema (Winograd, 1977; Billmire *et al.*, 1996). In the Billmire study, a 4-week-old infant was exposed to 5% pepper spray after discharge from a self-defense device. The infant suffered respiratory failure and hypoxemia, requiring immediate extracorporeal membrane oxygenation. Inhaled capsaicin causes an immediate increase in airway resistance (Fuller, 1991). This dose-dependent bronchoconstriction after capsaicin inhalation in humans is the same as that demonstrated in asthmatics and smokers (Fuller *et al.*, 1985). The capsaicin-induced bronchoconstriction and release of substance P is due to stimulation of nonmyelinated afferent C-fibers.

E. Neurologic Toxicity

RCAs are irritants to the peripheral nervous system (Anonymous, 1999). CN and CS interact with receptors on sensory nerves in the eyes, other mucous membranes, and skin, resulting in discomfort and burning pain. Their neurologic toxicity can range from paresthesias of the lips to burning pain of the eyes (ophthalmodynia), tongue (glossalgia), nose (rhinodynia), throat (pharyngodynia), and skin (dermatalgia). The reaction of CN with sulfhydryl (SH)-containing proteins and enzymes is the cause of denaturation associated with sensory nerve activity (Chung and Giles, 1972). As RCAs affect the senses, the feeling can become disorienting after exposure, which may explain why some experience temporary loss of balance and orientation after exposure (Thorburn, 1982).

Agitation and panic may develop in those not previously exposed to CN (Beswick, 1983; Stein and Kirwan, 1964). Syncope has also been reported (Athanaselis *et al.*, 1990; Thorburn, 1982), but this is likely attributed to panic. Headaches have been reported in 48% of symptomatic persons exposed to chloropicrin (Goldman *et al.*, 1987). When CN was released into 44 prisoner cells, eight inmates experienced malaise and lethargy and among those hospitalized, one experienced syncope and a severe systemic illness (Thorburn, 1982).

A clinical case report of hand injuries caused by accidental discharges from tear gas pens (Adams *et al.*, 1966) revealed specific neuronal toxicological findings. In each case, CN penetrated into the skin to cause a wound. Neurological examination indicated hyperesthesia of select digits in all cases. Biopsies of digital neurons taken for pathology showed thickened epineurium and tendon sheaths. Some of the patients complained of paresthesias months after exposure. The study suggests a possible link between direct chemical injury and nerve damage. The same investigators exposed the sciatic nerves of rabbits to agent by discharge of a CN pen or by dusting the exposed nerve with 0.2 g CN powder. These animal studies suggested CN can cause inflammation and necrosis in skeletal muscle, loss of axon cylinders, and replacement of neural elements with granulation tissue and fibroblasts (Adams *et al.*, 1966). Animals exposed to CR exhibit fasciculations, tremors, convulsions, and ataxia; intraperitoneal administration of CR can also cause muscle weakness (Salem *et al.*, 2006).

Capsaicin activates receptors in trigeminal (cranial nerve V) and intestinal neurons. These include pain receptors located in the mouth, nose, stomach, and mucous membranes. Trigeminal neurons utilize substance P as their primary pain neurotransmitter. Capsaicin first induces the release of substance P from the neuron and then blocks the synthesis and transport of substance P to the effector side (Bernstein *et al.*, 1981; Tominack and Spyker, 1987). Substance P depolarizes neurons to produce dilation of blood vessels, stimulation of smooth muscle, and activation of sensory nerve endings (Helme *et al.*, 1987; Tominack and Spyker, 1987). Jancso characterized the effects of capsaicin as an initial intense excitation of sensory neurons followed by a lengthy period of insensitivity to physicochemical stimuli (Jancso *et al.*, 1968, 1987; Buck and Burks, 1986). Substance P is associated with sensory (pain) or skin inflammation afferents. It is also a peripheral mediator of neurogenic inflammation and smooth muscle contraction (Lembeck and Holzer, 1979; Pernow, 1983). It contributes to contraction of the esophagus, trachea, respiratory tract, and levator palpebrae muscles (blepharospasm and apraxia of eyelid opening). Capsaicin directly applied to the eye causes a neurogenic inflammation, involving vasodilatation and extravasation of fluid, and unresponsiveness to chemical stimuli. Capsaicin renders the skin of humans and animals insensitive to various types of painful chemical stimuli (Bernstein *et al.*, 1981). In humans, OC exposure eventually causes loss of the corneal blink reflex (Olajos and Salem, 2001), which is mediated by sensory input from cranial nerve V and motor output via cranial nerve VII.

F. Gastrointestinal Toxicity

Many reviews state that gastrointestinal effects do not occur upon inhalational exposure to RCAs with the exception of DM; however, nausea, vomiting, and alterations in taste are commonplace in clinical case reports of exposure to CS (Solomon *et al.*, 2003; Athanaselis, 1990) and CN (Thorburn, 1982; Blain, 2003). The involvement of retching and emesis tends to occur if the individual is sensitive, the concentration is sufficiently high, the exposure prolonged, the range is close, or the event occurs in a confined space. Vomiting was reported in 25% of patients with severe reactions to CN in a confined area (Thorburn, 1982). Emesis did not resolve until the following week in one patient. Inhalation of RCAs often leads to parageusias or altered taste of the tongue. In particular, a metallic or burning sensation is often reported (Folb and Talmud, 1989).

Ingestion of CS can also produce episodes of nausea, vomiting, crampy abdominal pain (Blain, 2003), and diarrhea (Blain, 2003; Solomon, 2003). Seven patients in the Solomon study drank juice contaminated with CS pellets and primarily developed gastrointestinal symptoms. Two of the seven patients reported emesis and diarrhea; all patients reported abdominal pain, epigastric discomfort, and burning gastroesophageal reflux. Symptoms resolved 24 h later. Surprisingly, they did not develop parageusia or burning of the tongue after CS ingestion which is often the case after inhalational CS exposure. Another study designed for patients to taste an admixture of sugar and CS (5–10 pellets, 500 mg each and dissolved in 10 liters of water) indicated that patients experienced a 30 s delay in onset of altered taste (Kemp and Willder, 1972); this was most likely due to a masking effect from the sugar. In animal studies, rabbits and rats develop gastroenteritis upon CN or CS exposure by ingestion (Gaskins *et al.*, 1972).

Biting and ingesting *Capsicum* plants can cause nausea and vomiting (Morton, 1971; Tominack and Spyker, 1987; Snyman *et al.*, 2001). Nausea has also been reported in individuals exposed to pepperball tactical powder containing capsaicin (Hay *et al.*, 2006). Capsaicin causes effects on gastric mucosa including mild erythema, edema, epithelial cell damage (Desai *et al.*, 1976), and gastric hemorrhage (Viranuvatti *et al.*, 1972; Desai *et al.*, 1977; Kumar *et al.*, 1984).

G. Dermatological Toxicity

CN and CS are primary irritants of the integumentary system able to cause first and second degree burns (Stein and Kirwan, 1964; Weigand, 1969; Hu *et al.*, 1989). Low concentrations of either agent cause erythema, pruritis, subcutaneous edema, paresthesias, and/or burning sensations in exposed areas of the skin within minutes. Erythema is often the first sign of contact dermatitis, occurring minutes after exposure and subsiding about an hour after exposure. These agents follow a time course of skin damage similar to mustard agent. Further, if the skin is wet or abraded, the toxic effects on the skin are more prominent (Holland and White, 1972; Thorburn, 1982; Sidell, 1997). Exposure to higher doses leads to worsening erythema, edema, vesication with bullae (observed hours later), and fever. The extent of toxic effects also depends on thickness of the stratum corneum and time of exposure. Furthermore, contact with water up to 48 h after exposure can exacerbate the painful symptoms (Pinkus, 1978; Blain, 2003). High humidity, diaphoretic subjects, and warm temperatures can all exacerbate the contact dermatitis from RCAs (Hellreich *et al.*, 1969). Areas of occlusive dress over the skin may also result in worse reactions.

Higher concentrations of CS or longer exposures will result in more than erythema, pruritis, and burning pain. Papulovesicular rashes are not uncommon with high concentrations of RCAs. Typically, edema and vesiculation (bullae dermatitis) follow 24 h after CS or CN exposure (Sidell, 1997). Common sites of bullae are areas under the cuff of a shirt or glove and just under the collar. One study examined the effect of high CS concentrations (300 mg/m^3), tested on the arms of volunteer study patients, at times ranging between 15 and 60 min exposure (Hellreich *et al.*, 1967). All participants experienced burning pain approximately 5 min after exposure onset. A C*t* range of 4,440 and 9,480 mg.min/m^3 caused an immediate patchy erythema, which subsided after 30 min. A C*t* range of 14,040 and 17,700 mg.min/m^3 led to greater dermal toxicity and required several hours to subside. Bullous dermatitis occurred in 50% of subjects as a delayed reaction. These bullous lesions resolved in 2 weeks, but an inflammatory hyperpigmentation of the skin remained by 6 weeks post-exposure. Differences in individual sensitivities are due to skin pigmentation, complexion, and susceptibility to sunburns (Hellreich *et al.*, 1969).

Exposure to other RCAs causes similar dermal effects. CN is a more potent irritant than CS. In a human study involving dermal application, CN (0.5 mg) powder caused irritation and erythema when on the skin for 60 min (Holland and White, 1972). It took 20 mg CS to cause similar effects for the same duration of exposure. Exposure to 5% capsaicin pepper spray causes immediate and severe erythema and edema in the skin (Herman *et al.*, 1998). Similarly, pepper ball pellets fired at individuals will cause erythema, pain, and edema at the site of impact. The initial point of contact may become infected, scar, or heal with hyperpigmentation (Hay *et al.*, 2006).

Dermal exposure to CN or CS may lead to an allergic contact dermatitis (Madden, 1951; Penneys, 1971), a delayed hypersensitivity reaction developed from a previous exposure to RCAs. CS and CN are both skin sensitizers, but CN is more potent (Chung and Giles, 1972). Initial exposure to either may not cause significant toxic signs or symptoms. Exposure to small amounts of the same agent years later, however, may produce a severe allergic erythematous, patchy rash with edema, bullae, purpura, and necrosis. Sensitization is likely to occur after dermal exposure to high concentrations of RCAs (Penneys *et al.*, 1969; Holland and White, 1972; Leenutaphong and Goerz, 1989). Hypersensitivity reactions can persist for up to 4 weeks (Leenutaphong and Goerz, 1989). This phenomenon has been demonstrated so far by CN (Ingram, 1942; Kissin and Mazer, 1944; Steffen, 1968; Frazier, 1976) and CS (Ro and Lee, 1991) but not CR.

Dermal exposure to CR causes a burning sensation and erythema several minutes later. Burning pain goes away after 15 to 30 min, but the erythema lasts up to 2 h (Holland, 1974). CR does not induce inflammatory cell migration to the site of injury, bullous dermatitis, or contact sensitization (Ballantyne, 1977a). Repeated application of CR to the skin (applied 5 days/week for 12 weeks) has little effect (Marrs *et al.*, 1982). Similar to the eye and lungs, CR does not demonstrate significant toxicity to the skin.

CS, CN, or CR can pose a toxic danger hours after dissemination as they are persistent in the environment. During the riots of the late 1960s, CS was frequently used to control crowds. Inadvertently, firefighters in those metropolitan areas sometimes were exposed as they entered buildings where CS had been disseminated. The force of water from firehose and movement within the buildings reaerosolized enough agent toxic enough to cause erythema and edema around their eyes and other areas of exposed skin (Rengstorff and Mershon, 1969a).

While capsaicinoids may have a vesicant effect, depending on length of exposure, in most cases it produces a burning sensation and mild erythema. Capsaicins cause erythema and burning pain without vesiculation when applied topically to human skin (Smith *et al.*, 1970; Burnett, 1989; Watson *et al.*, 1996; Herman *et al.*, 1998). Skin blistering and rash may occur after chronic or prolonged capsaicin exposures (Morton, 1971).

H. Other Toxicity

One report noted renal tubular nephritis in a worker killed after an explosion inside a plant manufacturing CS agent (Cookson and Nottingham, 1969). Hepatocellular injury has been linked to serious CS inhalation (Krapf and Thalmann, 1981). To date, animal studies have not documented any relationship between RCA exposure and teratogenicity (Himsworth *et al.*, 1971; Upshall, 1973; Folb and Talmud, 1989). CS did not demonstrate mutagenic potential with the Ames assay (Rietveld *et al.*, 1983). Similarly, CR did not have carcinogenic effects in mice or hamsters (Blain, 2003); CS lacks mutagenicity in several test systems (Daniken *et al.*, 1981; Wild *et al.*, 1983).

I. Lethality

Human deaths have been reported from RCA exposure (Thorburn, 1982; Ferslew *et al.*, 1986; Danto, 1987). Death is usually the result of excessive concentrations used, confined spaces, and prolonged exposures. Death occurs hours after initial exposure, and post-mortem findings are consistent with severe airway damage seen in animals. Deichmann and Gerarde (1969) reported a fatality following exposure to high CN vapor concentrations (5.4 gm in a 34 m^3 room) for less than 20 min, which equates to approximately 160 mg/m^3. Estimates of the human LCt_{50} range between 25,000 and 150,000 $mg \cdot min/m^3$ for CS and between 8,500 and 22,500 $mg \cdot min/m^3$ for CN (Olajos and Salem, 2001). High doses of CR aerosol do not produce lethality in animals; CR aerosols of 68,000 $mg \cdot min/m^3$ are not lethal in mice, guinea pigs, or rabbits. The large safety ratio for CR is clearly evident as compared to the other agents.

While OC is widely regarded as a safe substance with low toxicity (Clede, 1993), more research should be conducted in light of recent deaths involving pepper spray use by law enforcement agencies. One case involving an inmate who died in custody implicated pepper spray as a direct contributor to death (Steffe *et al.*, 1995). Billmire *et al.* (1996) reported the life-threatening effects in a 4-week-old infant exposed to OC spray as a result of an accidental discharge.

VII. RISK ASSESSMENT

The ideal process in RCA risk assessment is to characterize the effectiveness and risk from exposures to situations where RCAs may be used (NAS, 1983, 1984; NAS/NRC, 1994; TERA, 2001; Patterson *et al.*, 2004). In order to do that, one must identify all pertinent effects of the RCA in question, develop a dose–response assessment, consider an exposure assessment, and finally characterize the risk. When used as intended, RCAs are thought to be safe and of sufficient low toxicity. They are designed with the purpose of disabling a targeted individual through sensory irritation of the eyes, respiratory tract, and skin. As discussed previously, they are not without additional, unwanted effects especially in circumstances where high concentrations are used or exposure is prolonged. The previous sections have provided sufficient discussion regarding the potential toxicity to humans as a result of exposure to RCAs, including case reports.

A. Identification of Intended and Unintended Effects

By providing a minimal force alternative for controlling and managing individual(s), RCAs are a desired public health and safety tool for military, domestic law enforcement, and civilian use. As with any chemical intended to benefit the public, it is important first to identify the compounds, their potential adverse impact (unintended effects), and their beneficial impact (intended effects). There are a number of chemicals designed and used as RCAs. In general, they are compounds with low vapor pressures and dispersed as fine particles or in solution from a variety of devices. These dispersal methods can include the gamut from aerial spray (Figure 12.6) to large spray tanks (see Figures 12.2 and 12.4) and small, hand-held devices for self-protection. The modern RCAs used today include CN, CS, CR, OC, and PAVA. Their major adverse effects are summarized in Table 12.2. The intended effect for all RCAs is a change in behavioral response of the target. A better measure of this intended effect would be the actual physiological effects produced by RCAs on the eyes, skin, and respiratory tract (Patterson *et al.*, 2004). These are the target organs designed for harassment by RCAs (see Figure 12.11 for review).

Each physiological effect can be evaluated and categorized on a broad spectral continuum from mild to severe. At lower aerosol dosages, the effects from RCAs will be reversible with no serious injury. For instance, typical mild ophthalmic effects include lacrimation (tearing) and transient burning pain (ophthalmodynia). When used at higher levels, in confined spaces and/or for prolonged duration, there is a greater potential for the toxicity to escalate. Moderate effects would include conjunctivitis, keratitis, blepharitis, chemosis, and periorbital edema. Severe effects result from significantly prolonged duration or high concentrations leading to irreversible damage in the tissues (i.e. loss of vision). These include corneal abrasions, scarring, or opacification. Very serious effects on the eye include symblepharon, pseudopterygium, cataracts, hyphema, posterior synechia, secondary glaucoma, vitreous hemorrhage, and traumatic optic neuropathy. The same analysis can be applied to effects on the skin, respiratory tracts, and additional organ systems affected for each agent.

B. Dose Response

Dose–response assessment involves evaluating the dose required to produce a particular effect of interest. Ideally,

quantitative data on specific doses and their corresponding responses are desired. In reality, threshold data for a particular target organ or effect in a target organ are often available as a substitute. The ophthalmic threshold levels and toxicity estimate for human responses to CN, CS, and CR are shown in Table 12.2. If empirical dose–response data are available, a dose–response evaluation for a given RCA might include plotting the percent of individuals responding as a function of dose for each toxicological sign or symptom and target organ of interest. Dose–response curves can then be used in modeling studies to estimate the probabilities of intended and unintended effects for a particular risk assessment scenario (Patterson *et al.*, 2004).

C. Exposure Assessment

The crux of exposure assessment is creating a scenario for human exposure to a given RCA and identifying the exposure factors. This would involve describing the intended target(s), environmental conditions (windy, rainy weather, etc.), crowd size and characteristics, delivery device (tear gas canisters or grenades, powder or aerosol), hazards associated with the delivery system like blunt trauma, as well as the nature of the agent selected (physicochemical properties, solvents, concentration/dose), and duration of exposure. An exposure assessment might include estimation of the amount of systemic exposure through RCA inhalation, absorption through the skin from dermal contact, or intestinal uptake after ingestion. Availability of quality data for each of the aforementioned exposure factors will estimate exposure with high confidence and minimal uncertainty level. Unavailability of data is a major limitation if models are used to estimate exposure.

D. Characterization of the Risk and Risk Management

Estimating or developing probabilities of toxic effects within a population is at the heart of risk characterization. It integrates dose–response and exposure assessments. It is designed to provide the probability of occurrence for effects induced by a given RCA given a particular exposure scenario. For example, a decision-maker will use risk characterization to estimate the probability of a group of effects occurring as a result of clearing a confined space with CS. The probability can be derived as a function of the number of tear gas grenades employed. Unfortunately, there is a dearth of specific Federal risk assessment and risk management guidance or mandates on RCAs. Therefore, the potential for risk management or mitigation of concerns is not optimized for the health and benefit of the public good (Hauschild, 2004). This is partly due to the fact that the process for assessing risk of toxic chemicals has yet to be standardized among Federal programs (Burke *et al.*, 1993; Rhomberg, 1997). Computer modeling to aid risk assessment without empirical data to feed the model can be an academic exercise. The two in combination can be a powerful predictor for risk assessment of any toxic chemical.

VIII. TREATMENT

Exposure to RCAs leads to a generalized stress reaction, causing leukocytosis (Thorburn, 1982; Park and Giammona, 1972), hypokalemia, elevated total protein, increased globulin, and high bicarbonate levels (Beswick *et al.*, 1972). Treatment for RCA toxicity is not often required since the course of intoxication is self-limiting for the most part. Serum toxicological testing is not available to detect RCAs (Sidell, 1997). Clinical signs and symptoms from RCA exposure subside in less than an hour. Initial care involves removing the victim from a potentially crowded area of dispersal immediately to minimize exposure time. It is important to note that these victims may require additional assistance during evacuation because of their reduced vision and disorientation. In circumstances where the concentration of agent is substantially elevated or the area of release is confined, increased complications and risks of morbidity may arise in the eyes, skin, airways, and lungs.

A. Eyes

If the eyes are involved to any degree, a protective mechanism to close the eyelids will be initiated as a result of conjunctivitis, iritis, or keratitis. Photophobia, blepharospasm, and apraxia of eyelid opening prevent the clinician from evaluating the damage. However, a local anesthetic applied to the eye will help with eye pain and allow for further evaluation of the eye by slit lamp. Contact lenses should be immediately removed and the eyes flushed of any dusting or agglomerated solid particles (see Figure 12.12). Eyes should be irrigated with copious volumes of water or saline for at least 15 min to adequately flush the irritant. Diphoterine has also been used to decontaminate eyes and skin after CS tear gas exposure (Viala *et al.*, 2005). If symptoms or signs of eye toxicity persist, consultation with an ophthalmologist is critical. Elderly patients should be monitored for evidence of possible acute glaucoma (Yih, 1995).

B. Skin

Early signs of skin toxicity at the time of clinical presentation will often be contact or allergic dermatitis since blisters form hours later. Removal of clothing should be the first step in decontamination. Placement of contaminated clothes in sealed plastic bags by first responders will prevent secondary contamination as a result of reaerosolized agent (Horton *et al.*, 2005). Early studies of CS indicated that mixing CS with sodium hypochlorite (or household bleach) produced a greater reaction than CS alone in patch testing

(Punte *et al.*, 1963). Despite its usefulness as a decontaminant for many chemical agents, hypochlorite should never be used to decontaminate RCAs on skin. Use of water for decontamination of skin may result in an initial worsening of the burning sensation (described previously). A solution of 6% sodium bicarbonate, 3% sodium carbonate, and 1% benzalkonium chloride has been shown to provide immediate relief from CS dermatitis as the alkaline solution hydrolyzes the agent (Weigand, 1969; Sidell, 1997). Consultation with a burn unit should be considered when large areas of skin are involved or when children are affected. Medical treatment for dermatitis may include topical steroids such as triamcinolone acetonide (Hellreich, 1967; Sidell, 1997), oral antihistamines for pruritis, and topical antibiotics such as silver sulfadiazine (Hellreich, 1967; Roberts, 1988). Systemic antibiotics can be given for secondary infection. Oozing lesions from bullae dermatitis should be treated with wet dressings, changed daily. Deroofing closed vesicles is controversial (Carvajal and Stewart, 1987; Roberts, 1988). Tetanus prophylaxis should be considered.

C. Respiratory

Removing an exposed patient from the source of intoxication to fresh air will provide immediate improvement. Patients should be evaluated for hypoxia with pulse oximetry and arterial blood gases. Pulmonary function tests may be helpful in patients with prolonged pulmonary complaints and followed until symptoms resolve. Chest radiography might be useful if concentration was sufficiently high, exposure was prolonged, or dispersal occurred in a confined space. Pulmonary edema may be delayed for 12 to 24 h after exposure, suggesting a need for follow-up radiographs (Stein and Kirwan, 1964; Solomon, 2003). Laryngospasm is a serious complication that may require tracheal intubation to secure a patent airway. Bronchospasm may be treated with inhaled beta-2 agonists, steroids (methylprednisolone), and aminophilline (Ballantyne and Swanston, 1978; Folb and Talmud, 1989). Arterial blood gas (Vaca *et al.*, 1996) and pulse oximetry should be continued if patients are symptomatic hours after exposure.

IX. CONCLUDING REMARKS AND FUTURE DIRECTION

The goal of RCAs is to harass or produce temporary incapacitation. Use of irritants to harass enemies dates back several thousand years. Today, law enforcement agencies and military personnel use RCAs for quelling protestors, controlling crowds, subduing combatants, clearing buildings, training in chemical warfare, and area denial. Individuals use hand-held devices for self-protection against an assailant. RCAs are dispersed as aerosols or sprays, causing irritation of mucous membranes of the eyes, respiratory tract, and skin. Symptoms and signs of toxicity typically subside by 30–60 min.

Several lines of evidence suggest that RCAs are safe if used as they were originally intended. Even though RCAs are considered safe, nonlethal, temporary incapacitating agents, they are not without risk. Some of the adverse clinical effects from RCA exposure reported in the literature have involved indiscriminate use (excessive concentrations), prolonged exposure, and dissemination of compound in a confined space. In short, these nonlethal agents can pose a serious health hazard in their intended targets. Some RCAs have such a poor safety profile that they have been abandoned long ago (DM and CA). CN and CS have a large body of literature from which to compare and contrast their safety, toxicity, and potency. As the data clearly suggest, CS is a safer compound to use compared to CN. The latest newcomers to the RCA scene are the inflammatory capsaicinoids. OC and PAVA are highly effective irritants that cause similar symptoms to CN and CS. Capsaicinoids gained considerable attention in the 1990s from police departments and the public at large for safe, effective chemical incapacitation of individuals. These compounds are primarily used as defensive sprays by law enforcement to subdue a combative suspect or by individuals for self-protection. While OC, PAVA, and related capsaicinoids produce a similar constellation of toxic signs and symptoms, they are not currently used to control crowds at the level of a riot. If OC-containing pepper spray is preferred for riot control, more research will be required to determine whether it is indeed safe for humans. Finally, risk assessment is a process which can identify gaps in the literature and therefore serves to highlight research needs.

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